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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/345,761	07/01/1999	TAKAHIKO ISHIGURO	Q54969	1618

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EXAMINER	
TAYLOR, JANELL E	

ART UNIT	PAPER NUMBER
1634	30

DATE MAILED: 09/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/345,761	Applicant(s) ISHIGURO ET AL.	
	Examiner Janell Cleveland Taylor	Art Unit 1634	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30,32-34,36-48 and 50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,32-34,36-48 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

The following office action is **FINAL**. Any rejection not reiterated is withdrawn. A "Response to Arguments" section follows.

Claim Rejections - 35 USC 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).6.

Claims 30, 32-34, 36-40, 44 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davey et al. (Davey, herein) (5,409,818, filing date June 24, 1988) in view of Olson et al. (Olson, herein) (WO 91/04340, April 4, 1991). Regarding claims 30

and 44, Davey et al. (5,409,818, April 1995) teach a method for assay a single-stranded target RNA molecule at a relatively constant temperature and without serial additions of reagents but in functional combination, or all at once, comprising the steps of (A) providing a single reaction medium containing reagents comprising: (i) a first oligonucleotide primer, (ii) a second oligonucleotide primer comprising an antisense sequence of an RNA polymerase promoter, (iii) a DNA-directed RNA polymerase that recognizes said promoter, (iv) an RNA-directed DNA polymerase, (v) a DNA-directed DNA polymerase, (vi) ribonucleoside and deoxyribonucleoside triphosphates; then (b) providing in said reaction medium RNA comprising an RNA first template which comprises said specific nucleic acid sequence or a sequence complementary to said specific nucleic acid sequence, under conditions such that a cycle ensues wherein (1) said first oligonucleotide primer hybridizes to said RNA first template, (ii) said RNA-directed DNA polymerase uses said RNA first template to synthesize a DNA second template by extension of said first oligonucleotide primer and thereby forms an RNA-DNA hybrid intermediate, (iii) said ribonuclease hydrolyzes RNA which comprises said RNA-DNA hybrid intermediate (iv) said second oligonucleotide primer hybridizes to said DNA second template, (v) said DNA-directed DNA polymerase uses said second oligonucleotide primer as template to synthesize a functional RNA polymerase promoter by extension of said DNA second template and (vi) said DNA-directed RNA polymerase recognizes said functional promoter and transcribes said DNA second template, thereby providing copies of said RNA first template; and thereafter (c) maintaining said conditions for time sufficient to achieve a desired amplification of said specific nucleic

acid sequence (column 5, lines 26-68 and column 6, lines 1-6). Davey further teach a probe labeled with a fluorophore (col. 9, lines 5-7 and 34-36) and an additional step of detecting or quantifying the single-stranded RNA in the sample based on the measured fluorescent signal or change in the measured fluorescent signal (column 8, lines 54-65). Davey teaches that is assay method is advantageous because it requires less participation and fewer manipulation by the user.

The single-stranded RNA assay method of Davey differs from the claimed invention in that Davey does not teach a reagent (A) which allows the single-stranded RNA to be cut at the 5' end of the specific nucleic acid sequence nor does the reference teach wherein the oligonucleotide containing the promoter sequence includes an enhancer sequence for the promoter. The Examiner however takes notice that enhancer sequences were routinely used in the prior art with promoter sequences to increase the level of transcription. In a method similar to that of Davey et al. for assaying target DNA or RNA of interest, Olson teaches wherein the target nucleic acid is exposed to a reagent which allows the target nucleic acid to be cut at the 5' end of the specific nucleic acid sequence and wherein the product from the cutting step is hybridized to a primer complementary to a sequence at the 3' end of the specific nucleic acid sequence (page 5, beginning at line 16 to page 6, line 33).

Olson et al. further teach that the target sequence is cut to isolate the region of interest having a defined 3' end available for hybridization (page 5, lines 27-33 and page 22, lines 21-33). In view of the foregoing, it would have been obvious to one of ordinary skill in the art to have been motivated to incorporate an agent which cuts the target

nucleic acid at selected sites as taught by Olson in the method of assaying for a target nucleic acid as taught by Davey for the benefit of producing a specific target nucleic acid at a selected site for analysis by hybridization and amplification as suggested by Olson.

Regarding claim 32, Davey et al. teach wherein a reagent which is DNA is added to the method and wherein the method further comprises a step of adding RNAase H and a subsequent step of deactivating the RNAase H by heating or by the addition of an inhibitor prior to addition of the reagent (b) (column 6, line 19 and column 8, lines 20-33).

Regarding claims 33 and 34, Davey et al teach wherein the reagents are added sequentially and simultaneous (column 8, lines 35-37 and lines 54-62).

Regarding claim 36, Davey teaches wherein the enzyme which degrades RNA in a DNA-RNA double strand is the RNA-dependent DNA polymerase reagent (column 5, lines 26-35).

Regarding claim 37, Davey teaches wherein an enzyme having both an RNA-dependent DNA polymerase activity and a DNA-dependent DNA polymerase activity is used as two separate reagents (column 7, lines 48-68 and column 8, lines 1-19).

Regarding claim 38, Davey teaches wherein the enzyme is avian myoblastome virus polymerase (column 7, lines 53-55).

Regarding claim 39, Davey teaches wherein two reagent in the method identified as reagents (b) and (F) are used at concentrations of from 0.02 to 1 micro molar (column 17, example 8, line 35).

Regarding claim 40, Davey teaches wherein the DNA-dependent RNA polymerase as the reagent (H) is either phage SP6 polymerase, phage T3 polymerase or the phage T7 polymerase (column 7, lines 38-41).

Regarding claim 50, Davey discloses utilizing relatively constant temperature for the amplification process of about 42 degrees Celsius (examples 3-9 columns 15-17).

The order of combination of method steps as described in the instant claims are not critical to the claimed invention. *In re Burhans*, 69 USPQ 330 states that a selection of any order of performing process steps is **prima facie** obvious in the absent of new or unexpected results.

7. Claims 41-43 rejected under 35 U.S.C. 103(a) as being unpatentable over Davey as described above, in view of Ishiguro et al. (Ishiguro, herein) (6,063,572 filing date January 23, 1998).Regarding claims 41-43, Davey in view of Olson teach a method of assaying a specific nucleic acid sequence using an amplification process as discussed earlier. The method of Davey in view of Olson et al. differs from the claim invention in that the references do wherein the not teach using an intercalative fluorescent dye as one of the reagents involved in fluorescent labeling. Ishiguro teaches a method of assaying a specific nucleic acid comprising: (a) adding to a sample an oligonucleotide primer, wherein the nucleotide sequence of the primer is complementary to the target nucleic acid sequence and comprises a RNA polymerase promoter sequence, wherein a duplex is formed between the target nucleic acid and the primer when the target sequence is present in the sample; (b) elongating the primer in a duplex with the target nucleic acid sequence in (a) to produce a double-stranded polynucleotide; (c) reacting

the double- stranded polynucleotide produced in (b) with RNA polymerase to produce RNA (d) adding an oligonucleotide probe complementary to the RNA in (c) wherein the probe is labeled with a fluorescent intercalative dye; (e) measuring the fluorescence of the intercalative dye (see claim 1 and abstract). Ishiguro teaches that the fluorescent intercalative dye as the label may be linked to any site of the nucleotide, including the 5' end, the 3'-end and the center, as long as the linkage neither hinders the fluorescent intercalative dye from intercalating to double-stranded DNA nor hinders the oligonucleotide from hybridizing with the RNA (col. 5, lines 54-59). Ishiguro teaches that the intercalative dye-labeled probe coexisting in the reaction solution enhances the fluorescent intensity in proportion to the amount of hybrid which makes it possible to detect the specific nucleic acid or determine the initial amount of the specific nucleic acid by measuring the fluorescent intensity of the reaction before and after, or during the detection step (col. 6, lines 44-51). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have been motivated to modified the method of assaying a target nucleic acid as taught Davey in view of Olson with the an intercalative fluorescent dye linked an oligo-DNA as taught in the method of assay a specific nucleic acid of Ishiguro. One of ordinary skill in the art would have been motivated to do so for the benefits taught by Ishiguro that an intercalative dye-labeled probe coexisting in a reaction solution enhances the fluorescent intensity in proportion to the amount of hybrid which makes it possible to detect a specific nucleic acid or determine the initial amount of a specific nucleic acid by measuring the

fluorescent intensity of the reaction before and after, or during the detection step (col. 6, lines 44-51).

8. Claims 45-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davey in view of Olson and further in view of Newton (PCR, Essential Data, 1995). Regarding claim 45, Davey in view of Olson teach a method of assaying a specific nucleic acid using an amplification process as described earlier. The claimed invention differs from the references in that they do not teach wherein all the reagents are chloride-free. In a guide for PCR, Newton discloses an amplification reaction buffer, wherein all the reagents are chloride-free (page 149, table 1, buffer #2). Newton further teaches an advantage of a chloride-free buffer is evident in the fact that some enzymes perform better in a PCR buffer than in their standard recommended buffer (page 144, column 1, second paragraph). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have been motivated to modify the reagents in the method of assaying a target nucleic acid at taught by Davey in view of Olson with the chloride-free reaction buffer of Newton for the expected benefits of maximizing enzyme activity based on Newton=s teaching that some enzymes perform better in a PCR buffer than in their standard recommend buffer (page 144, column 1, second paragraph).

Regarding claim 46, Newton teaches wherein acetate in used in the amplification reaction (page 149, table 1, buffer #2).

Regarding claim 47, Newton teaches using magnesium acetate at a concentration of 10 mM and using potassium acetate at a concentration of 66 mM (page 149, table 1, buffer #2).

9. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davey in view of Olson et al. and further in view of Cleuziat et al. (Cleuziat, herein) (5,824,517 filing date May 16, 1997). Davey in view of Olson teach a method of assaying a specific nucleic acid sequence using an amplification process as discussed earlier. The method of Davey in view of Olson differ from the claimed invention in that the references do not teach wherein sorbitol is added to the reaction. In a method similar to the method of Davey, Cleuziat discloses using an amplification reaction to assay nucleic acid sequences. Cleuziat further teaches wherein polyols such as sorbitol can be used in a reaction mixture to aid in accomplishing amplification. Cleuziat teach that such a reagent along with denaturing agents and stabilizing agents are useful for reducing non-specific hybridization reactions that could generate background noise (col. 9, lines 11-19). In view of the foregoing, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate sorbitol as taught by Cleuziat in the method of assaying a target nucleic acid as taught by Davey in view of Olson for the expected benefit of accomplishing amplification with a reduction in non-specific hybridization and background noise as suggested by Cleuziat.

Response to Arguments

Applicant's arguments filed August 16, 2002 have been fully considered but they are not persuasive. Applicant has argued that there is no motivation to combine the

references of Olson and Davey. Applicant states that although Olson disclose amplification of a target RNA, the RNA amplification disclosed by Olson does not involve cleavage of the target RNA. Applicant also states that Davey et al. do not teach or suggest detection of amplified target RNA, so even if Davey and Olson were combined, the present invention would not result. However, it would have been obvious to one of ordinary skill in the art to incorporate an agent which cuts the target nucleic acid at selected sites as taught by Olson in the method of assaying for a target nucleic acid as taught by Davey for the benefit of producing a specific target nucleic acid at a selected site for analysis by hybridization and amplification as suggested by Olson. In MPEP section 2144, it states that "the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also In re Kotzab, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); In re Nilssen, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); Ex parte Clapp, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and Ex parte Levengood, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)

(reliance on logic and sound scientific reasoning)." In the instant case, the knowledge was generally available to one of ordinary skill in the art to combine the teachings of Olson and Davey.

Conclusion

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiries of a general nature relating to this application, including information on IDS forms, status requests, sequence listings, etc. should be directed to the Patent Analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janell Taylor Cleveland, whose telephone number is (703) 305-0273.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (703) 308-1152.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed to Group 1634 via the PTO Fax Center using (703) 872-9306 or 872-9307 (after final). The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989.)

Janell Taylor Cleveland

September 12, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600